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(54) Title: HETEROINDANES: A NEW CLASS OF POTENT CANNABIMIMETIC LIGANDS

(57) Abstract: One aspect of the invention is concerned with cannabimimetic heteroindane analogs having affinities and/or selectivities for a cannabinoid receptor. A further aspect of the invention is concerned with pharmaceutical preparations employing the inventive analogs and methods of administering therapeutically effective amounts of the inventive analogs to provide a physiological effect.

HETEROINDANES: A NEW CLASS OF POTENT CANNABIMIMETIC LIGANDS

Field of the Invention

The present invention relates generally to compounds exhibiting cannabimimetic activity and is more particularly concerned with new and improved heteroindane analogs exhibiting high binding affinities for cannabinoid receptors, pharmaceutical preparations employing these compounds and methods of administering therapeutically effective amounts of these compounds to provide a physiological effect.

Background of the Invention

The classical cannabinoid Δ^9-Tetrahydrocannabinol (Δ^9-THC) is the major active constituent extracted from Cannabis sativa. The effects of cannabinoids such as Δ^9-THC are due to an interaction with specific high-affinity receptors. Presently, two cannabinoid receptors have been characterized: CB1, a central receptor found in the mammalian brain and a number of other sites in the peripheral tissues and CB2, a peripheral receptor found principally in cells related to the immune system. The CB1 receptor is believed to mediate the psychoactive properties, associated with classical cannabinoids. Characterization of these receptors has been made possible by the development of specific synthetic ligands such as the agonists WIN 55212-2 and CP 55,940.

In addition to acting at the cannabinoid receptors, some cannabinoids such as Δ^9-THC also affect cellular membranes, thereby producing undesirable side effects such as drowsiness, impairment of monoamine oxidase function and impairment of non-receptor mediated brain function. The addictive and psychotropic properties of some cannabinoids also limit their therapeutic value.

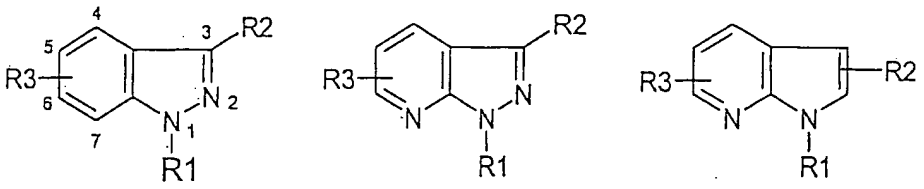
The pharmacological effects of cannabinoids pertain to a variety of areas such as the central nervous system, the cardiovascular system, the immune system and/or the endocrine system.

Summary of the Invention

Briefly stated, one aspect of the present invention comprises novel cannabimimetic ligands. The inventive compounds are encompassed by an indole

structure with one or more heteroatoms in one or both of the structure rings wherein at least one additional nitrogen atom is in the ring 2, 3, 4, 5, 6 or 7 position. Some advantageous embodiments of the invention are shown in compound formulas I, II or III. R2 may be in the 2 or 3 position where possible. Representative ring positions are shown in compound formula I.

I II III



R1 comprises –Q–Z.

Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present.

Z comprises, in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

In a variation of the invention R1 comprises –Q–Z.

Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present.

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom.

In a variation of the invention R1 comprises –Q–Z.

Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present.

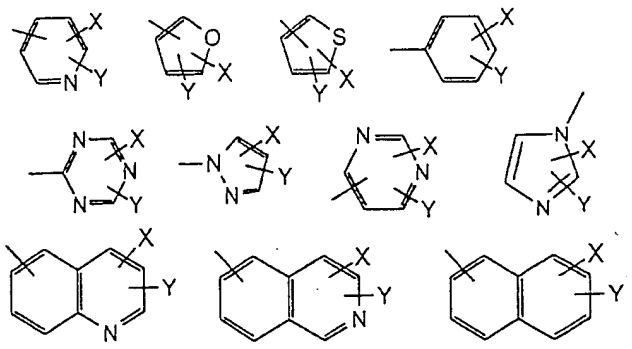
Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group comprising a substituent group on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom.

In one advantageous embodiment of the above variation Z comprises adamantyl or heteroadamantyl.

In a variation of the invention R1 comprises –Q–Z.

Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present.

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

R2 comprises $-Q_1-het-Q_2-Z$.

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

het comprises O, N or S.

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

Z comprises, in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

In a variation of the invention R2 comprises $-Q_1-het-Q_2-Z$.

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

het comprises O, N or S.

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom.

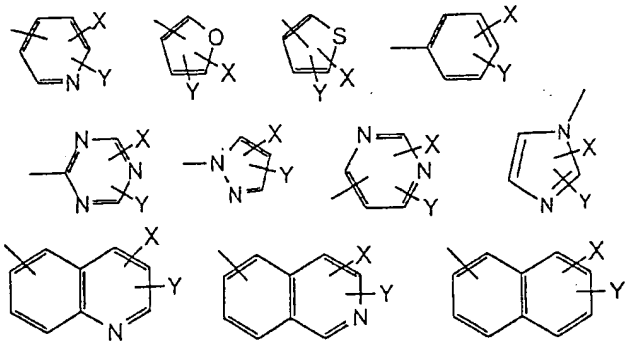
In a variation of the invention R2 comprises $-Q_1-het-Q_2-Z$.

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

het comprises O, N or S.

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

In a variation of the invention R2 comprises $-Q_1-het-Q_2-Z$.

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

het comprises O, N or S.

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom.

In one advantageous embodiment of the above variation Z comprises adamantyl or heteroadamantyl.

In a variation of the invention R2 comprises $-Q_1-X-Q_2-Z$.

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present and connected to a C, O or N atom in the X group.

X is optionally present and comprises any possible member selected from C(O), C(O)O, OC(O)O, NC(O)O, C(O)NT, NTC(O), OC(O)NT, C(O)NTT, C(O)NTNT, NTC(O)NT if present.

T comprises H, an alkyl group comprising 1 to about 4 C atoms, a heteroalkyl group comprising 1 to about 4 C atoms, a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members or a heteroaromatic ring having about 5 to about 7 ring members or any above group having a substituent group on at least one available ring atom.

Z comprises in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

In a variation of the invention R2 comprises $-Q_1-X-Q_2-Z$.

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present and connected to a C, O or N atom in the X group.

X is optionally present and comprises any possible member selected from C(O), C(O)O, OC(O)O, NC(O)O, C(O)NT, NTC(O), OC(O)NT, C(O)NTT, C(O)NTNT, NTC(O)NT if present.

T comprises H, an alkyl group comprising 1 to about 4 C atoms, a heteroalkyl group comprising 1 to about 4 C atoms, a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members or a heteroaromatic ring having about 5 to about 7 ring members; or any above group having a substituent group on at least one available ring atom.

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group;

or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom.

In a variation of the invention R2 comprises $-Q_1-X-Q_2-Z$.

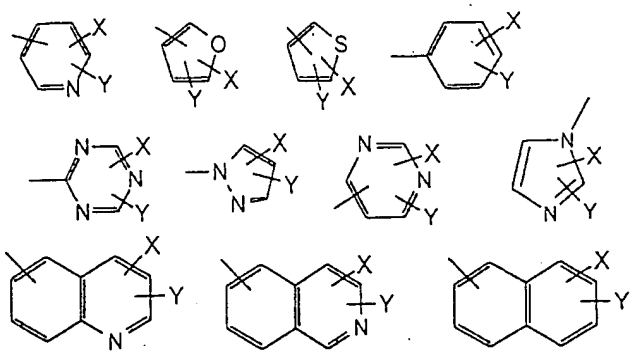
Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present and connected to a C, O or N atom in the X group.

X is optionally present and comprises any possible member selected from C(O), C(O)O, OC(O)O, NC(O)O, C(O)NT, NTC(O), OC(O)NT, C(O)NTT, C(O)NTNT, NTC(O)NT if present.

T comprises H, an alkyl group comprising 1 to about 4 C atoms, a heteroalkyl group comprising 1 to about 4 C atoms, a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members or a heteroaromatic ring having about 5 to about 7 ring members; or any above group having a substituent group on at least one available ring atom.

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

In a variation of the invention R2 comprises $-Q_1-X-Q_2-Z$.

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present.

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present and connected to a C, O or N atom in the X group.

X is optionally present and comprises any possible member selected from C(O), C(O)O, OC(O)O, NC(O)O, C(O)NT, NTC(O), OC(O)NT, C(O)NTT, C(O)NTNT, NTC(O)NT if present.

T comprises H, an alkyl group comprising 1 to about 4 C atoms, a heteroalkyl group having 1 to about 4 C atoms, a carbocyclic ring having

about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members or a heteroaromatic ring having about 5 to about 7 ring members; or any above group having a substituent group on at least one available ring atom.

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group comprising a substituent group on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom.

In one advantageous embodiment of the above variation Z comprises adamantyl or heteroadamantyl.

In one advantageous embodiment of the above variation Z comprises phenyl having independently selected substituent groups in at least one of the 2 and 5 positions.

In one advantageous embodiment of the above variation Z comprises phenyl substituted with a heteroaromatic moiety.

In one advantageous embodiment of the above variation Z comprises phenyl substituted in one of the 2 or 5 position with a heteroaromatic moiety and in the other of the 2 or 5 position with a halogen.

R3 comprises a substituent at any or all of the possible 4–, 5–, 6– and/or 7– positions. Each substituent is independently selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto,

alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

The inventive compounds include any and all isomers and steroisomers. In general, the compositions of the invention may be alternately formulated to comprise, consist of, or consist essentially of, any appropriate components herein disclosed. The compositions of the invention may additionally, or alternatively, be formulated so as to be devoid, or substantially free, of any components, materials, ingredients, adjuvants or species used in prior art compositions or that are otherwise not necessary to the achievement of the function and/or objectives of the present invention.

Unless otherwise specifically defined, "acyl" refers to the general formula –C(O)alkyl.

Unless otherwise specifically defined, "acyloxy" refers to the general formula –O–acyl.

Unless otherwise specifically defined, "alcohol" refers to the general formula alkyl–OH and includes primary, secondary and tertiary variations.

Unless otherwise specifically defined, "alkyl" or "lower alkyl" refers to a linear, branched or cyclic alkyl group having from 1 to about 16 carbon atoms including, for example, methyl, ethyl, propyl, butyl, hexyl, octyl, isopropyl, isobutyl, tert-butyl, cyclopropyl, cyclohexyl, cyclooctyl, vinyl and allyl. The alkyl group can be saturated or unsaturated. The alkyl group can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. Unless otherwise specifically limited, a cyclic alkyl group includes monocyclic,

bicyclic, tricyclic, tetracyclic and polycyclic rings, for example norbornyl, adamantyl and related terpenes.

Unless otherwise specifically defined, "alkoxy" refers to the general formula –O–alkyl.

Unless otherwise specifically defined, "alkylmercapto" refers to the general formula –S–alkyl.

Unless otherwise specifically defined, "alkylamino" refers to the general formula –(NH)–alkyl.

Unless otherwise specifically defined, "di-alkylamino" refers to the general formula $-N-(alkyl)_2$. Unless otherwise specifically limited di-alkylamino includes cyclic amine compounds such as piperidine and morpholine.

Unless otherwise specifically defined, an aromatic ring is an unsaturated ring structure having about 5 to about 7 ring members and including only carbon as ring atoms. The aromatic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "aryl" refers to an aromatic ring system that includes only carbon as ring atoms, for example phenyl, biphenyl or napthyl. The aryl group can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "aroyl" refers to the general formula –C(=O)–aryl.

Unless otherwise specifically defined, a bicyclic ring structure comprises 2 fused rings that include only carbon as ring atoms. The bicyclic ring structure can be saturated or unsaturated. The bicyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of bicyclic ring structures include naphthalene and bicyclooctane.

Unless otherwise specifically defined, a carbocyclic ring is a non-aromatic ring structure, saturated or unsaturated, having about 3 to about 8 ring members that includes only carbon as ring atoms, for example, benzene or cyclohexane. The carbocyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "halogen" refers to an atom selected from fluorine, chlorine, bromine and iodine.

Unless otherwise specifically defined, a heteroaromatic ring is an unsaturated ring structure having about 5 to about 8 ring members independently selected from carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, for example, pyridine, furan, quinoline, and their derivatives. The heteroaromatic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, a heterobicyclic ring structure comprises 2 fused rings having ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur. The heterobicyclic ring structure may be saturated or unsaturated. The heterobicyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heterobicyclic ring structures include isobenzofuran, indole, tetrahydroisoquinoline, tropane and homotropane.

Unless otherwise specifically defined, a heterocyclic ring is a saturated ring structure having about 3 to about 8 ring members independently selected from carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur; for example, piperidine, morpholine, piperazine, pyrrolidine, thiomorpholine, and their derivatives. The heterocyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, a heterotricyclic ring structure comprises 3 fused rings having ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur. The heterotricyclic ring structure may be saturated or unsaturated. The heterotricyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heterotricyclic ring structures include carbazole, phenanthroline and phenazine.

Unless otherwise specifically defined, a heteropolycyclic ring structure comprises more than 3 fused rings having ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur.

The heteropolycyclic ring structure is typically unsaturated. The heteropolycyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heteropolycyclic ring structures include azaadamantane, other heteroadamantanes, tropane and homotroapane.

Unless otherwise specifically defined, the term "optionally present" means that the specified moiety may or not be present in the recited structure. For example, if the recited structure is alkyl-V-W with V being optionally present, the recited structure comprises alkyl-V-W as well as alkyl-W.

Unless otherwise specifically defined, the term "phenacyl" refers to the general formula –phenyl–acyl.

Unless otherwise specifically defined, a polycyclic ring structure comprises more than 3 fused rings and includes carbon as ring atoms. The polycyclic ring structure can be saturated or unsaturated. The polycyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of polycyclic ring structures include adamantane, bicyclooctane, norbornane and bicyclononanes.

Unless otherwise specifically defined, a spirocycle refers to a ring system wherein a single atom is the only common member of two rings. A spirocycle can comprise a saturated carbocyclic ring comprising about 3 to about 8 ring members, a heterocyclic ring comprising about 3 to about 8 ring atoms wherein up to about 3 ring atoms may be N, S, or O or a combination thereof.

Unless otherwise specifically defined, a tricyclic ring structure comprises 3 fused rings and includes carbon as ring atoms. The tricyclic ring structure can be saturated or unsaturated. The tricyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. and may be substituted or unsubstituted. The individual rings may or may not be of the same type. Examples of tricyclic ring structures include fluorene and anthracene.

Substituent groups for the above moieties useful in the invention are those groups that do not significantly diminish the biological activity of the inventive compound. Substituent groups that do not significantly diminish the biological activity

of the inventive compound include, for example, H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3X_3, $PO_3X_1X_2$, $OPO_3X_1X_2$, $SO_2NX_1X_2$, $NCONX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, sulfonamide, thioalkoxy, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, aryl, substituted aryl, heteroaryl (including tetrazoles and alkyltetrazoles), substituted heteroaryl, phenyl, heterocyclic rings or methylene dioxy when the substituted structure has two adjacent carbon atoms, wherein X_1 and X_2 each independently comprise H or alkyl, or X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members and X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2. Unless otherwise specifically limited a substituent group may be in any possible position.

Some of the inventive compounds show high binding affinities for the CB1 and CB2 cannabinoid receptors. More specifically, some of the inventive analogs show similar or higher receptor binding affinity than the well-known indole cannabinoid WIN 55212-2. Thus, another aspect of the invention is use of at least one of the inventive compounds to interact with cannabinoid receptors.

Further, some of the inventive heteroindane analogs show a surprisingly higher selectivity for one of the cannabinoid receptors. These inventive selective analogs are able to interact with one cannabinoid receptor, for example the CB2 cannabinoid receptor, without affecting the other cannabinoid receptor to the same degree. Therefore, still another aspect of the invention is use of at least one of the inventive compounds to preferentially interact with one cannabinoid receptor.

Some of the novel heteroindanes described herein are cannabinoid receptor agonists. The inventive heteroindane agonists interact with the CB1 and/or CB2 cannabinoid receptor binding site to initiate a physiological or a pharmacological response characteristic of that receptor. Therefore, a further aspect of the invention is use of at least one of the inventive compounds to initiate an agonistic response from a cannabinoid receptor.

Some of the novel heteroindanes described herein are cannabinoid receptor antagonists. The inventive heteroindane antagonists interact with the CB1 and/or

CB2 cannabinoid receptor binding site to block other ligands from the receptor binding site without initiating a physiological or a pharmacological response characteristic of that receptor. Thus, cannabinoid antagonists typically oppose the cannabinoid receptor site response characteristics initiated by cannabinoid agonists or cannabinoid inverse agonists. Therefore, a further aspect of the invention is use of at least one of the inventive compounds to oppose initiation of an agonistic or inverse agonistic response from a cannabinoid receptor.

The inventive heteroindane analogs described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response in individuals and/or animals. Thus, another aspect of the invention is the administration of a therapeutically effective amount of at least one of the inventive compounds, or a physiologically acceptable salt thereof, to an individual or animal to provide a physiological response.

A better understanding of the invention will be obtained from the following detailed description of the article and the desired features, properties, characteristics, and the relation of the elements as well as the process steps, one with respect to each of the others, as set forth and exemplified in the description and illustrative embodiments.

Description of Some Preferred Embodiments

As used herein a "therapeutically effective amount" of a compound, is the quantity of a compound which, when administered to an individual or animal, results in a sufficiently high level of that compound in the individual or animal to cause a physiological response. Some physiological responses that result from cannabinoid receptor (CB1 and/or CB2) interaction with agonist or antagonist compounds include: relief of central pain; peripheral pain; inflammatory pain; neuropathy; alleviation of the symptoms of neurodegenerative diseases including multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease; alleviation of the symptoms of mental disorders such as schizophrenia and depression; reduction or prevention of endotoxic shock and hypotensive shock; appetite modulation; fertility reduction; reduction or prevention of diseases associated with motor function such as Tourette's syndrome; reduction or prevention of inflammation; neuroprotection;

suppression of memory; production of peripheral vasodilation; reduction of intraocular pressure in glaucoma; relief of nausea associated with cancer chemotherapy, enhancement of appetite in AIDS wasting syndrome; and reduction of spasticity in multiple sclerosis and epilepsy.

Typically, a "therapeutically effective amount" of an inventive compound is believed to range from about 5 mg/day to about 1,000 mg/day.

As used herein, an "individual" refers to a human. An "animal" refers to, for example, veterinary animals, such as dogs, cats, horses and the like, and farm animals, such as cows, pigs and the like.

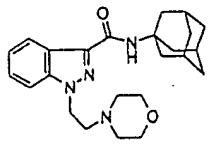
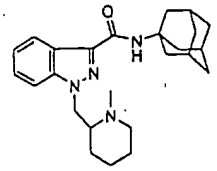
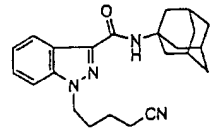
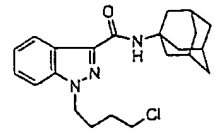
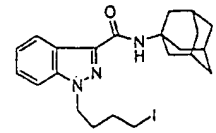
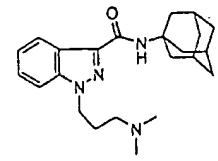
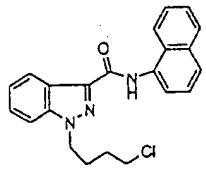
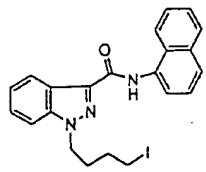
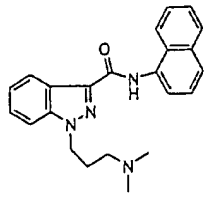
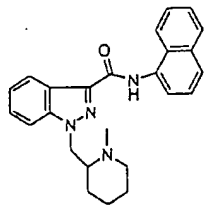
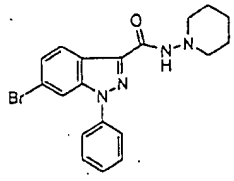
The compound of the present invention can be administered by a variety of known methods, including, for example, orally, rectally, transdermally or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to, capsular and tablet formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular, subcutaneous, ocular, intranasal, inhalation-based and transdermal administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically acceptable vehicles include, for example, saline, sterile water, Ringer's solution and isotonic sodium chloride solutions. The specific dosage level of active ingredient will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

The following examples are given for purposes of illustration only in order that the present invention may be more fully understood. These examples are not intended to limit in any way the scope of the invention unless otherwise specifically indicated.

Examples:

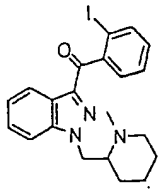
TABLE 1 illustrates some synthesized heteroindane analogs of the present invention (compounds 1-11).

TABLE 1

		Ki (nM) CB1	CB2
1		6.84	0.147
2		47.5	8.74
3		2.28	0.309
4		1.65	1.34
5		0.596	0.164
6		443	20.9
7		0.268	0.135
8		13.7	27.0
9		450.6	234.6
10		15.0	8.04
11		1846	84.7

Another synthesized heteroindane analog (12) is 1-(N-Methyl-2-

piperidinylmethyl)-3(2-iodobenzoyl) indazole.



KI (nM) : CB1 9.120; CB2 22.15

The inventive analogs were tested for CB2 receptor binding affinity and for CB1 receptor affinity (to determine selectivity for the CB2 receptor). As used herein, "binding affinity" is represented by the IC_{50} value which is the concentration of an analog required to occupy the 50% of the total number (Bmax) of the receptors. The lower the IC_{50} value the higher the binding affinity. As used herein an analog is said to have "binding selectivity" if it has higher binding affinity for one receptor compared to the other receptor; e.g. a cannabinoid analog which has an IC_{50} of 0.1 nM for CB1 and 10 nM for CB2, is 100 times more selective for the CB1 receptor. For the CB1 receptor binding studies, membranes were prepared from rat forebrain membranes according to the procedure of P.R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 107 - 118 (1981). The binding of the novel analogues to the CB1 cannabinoid receptor was assessed as described in W.A. Devane et al, Determination and Characterization of a Cannabinoid Receptor in a Rat Brain, Mol. Pharmacol., 34, 605 - 613 (1988) and A. Charalambous et al, 5'-azido Δ^8 - THC: A Novel Photoaffinity Label for the Cannabinoid Receptor, J. Med. Chem., 35, 3076 - 3079 (1992) with the following changes. The above articles are incorporated by reference herein.

Membranes, previously frozen at -80°C, were thawed on ice. To the stirred suspension was added three volumes of TME (25 mM Tris-HCl buffer, 5 mM $MgCl_2$ and 1 mM EDTA) at a pH 7.4. The suspension was incubated at 4°C for 30 min. At the end of the incubation, the membranes were pelleted and washed three times with TME.

The treated membranes were subsequently used in the binding assay described below. Approximately 30 µg of membranes were incubated in silanized 96-well microtiter plate with TME containing 0.1% essentially fatty acid-free bovine

serum albumin (BSA), 0.8 nM [^{3}H] CP-55,940, and various concentrations of test materials in a final volume of 200 mL. The assays were incubated for 1 hour at 30 °C and then immediately filtered using Packard Filtermate 196 harvester and Whatman GF/C filterplates and washed with wash buffer (TME) containing 0.5% BSA. Radioactivity was detected using MicroScint 20 scintillation cocktail added directly to the dried filterplates, and the filterplates were counted using a Packard Instruments Top-Count. Nonspecific binding was assessed using 100 nM CP-55,940. Data collected from three independent experiments performed with duplicate determinations was normalized between 100% and 0% specific binding for [^{3}H] CP-55,940, determined using buffer and 100 nM CP-55,940. The normalized data was analyzed using a 4-parameter nonlinear logistic equation to yield IC_{50} values. Data from at least two independent experiments performed in duplicate was used to calculate IC_{50} values which were converted to K_i values using the assumptions of Cheng et al, Relationship Between the Inhibition Constant (K_i) and the concentration of Inhibitor which causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction, Biochem. Pharmacol., 22, 3099-3102, (1973), which is incorporated by reference herein.

For the CB2 receptor binding studies, membranes were prepared from frozen mouse spleen essentially according to the procedure of P.R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 226, 107 - 118 (1981) which is incorporated by reference herein. Silanized centrifuge tubes were used throughout to minimize receptor loss due to adsorption. The CB2 binding assay was conducted in the same manner as for the CB1 binding assay. The binding affinities (K_i) were also expressed in nanomoles (nM). The cannabinoid receptor binding affinities (Ki) for synthesized analogs 1-11 are listed in TABLE 1.

Some inventive heteroindane analogs were also subjected to a GTPγS binding assay as described below. The GTPγS binding assay generally followed the procedures of S. Lin et al, Novel Analogues of Arachidonylethanolamide (Anandamide): Affinities for the CB1 and CB2 Cannabinoid Receptors and Metabolic Stability, J. Med. Chem., 41, 5353-5361 (1998) and M. A. K. Markwell et al, A Modification of the Lowry Procedure to Simplify Protein Determination in Membrane and Lipoprotein Samples, Anal. Biochem. 87, 206-210 (1978), the contents of which

are hereby incorporated by reference. The results indicated that all compounds tested were agonists for both the CB1 and the CB2 receptors.

The inventors believe that the novel heteroindane analogs when studied for their effects on the level of cyclic AMP in order to assess their functional potency as agonists or antagonists will confirm that the prepared compounds act as agonists.

Procedure for [^{35}S] GTPγS Binding Assay:

1. Cerebellar Membrane Preparation. The striped rat brains were slightly thawed, and using a spatula, the cerebellum was removed and discarded; the remaining tissue was homogenized in ice-cold homogenization buffer (0.32 M sucrose, 10 mM Tris, 5 mM EDTA, pH 7.4). The homogenate suspension was centrifuged at 3700g for 10 min. The supernatant was decanted, and 12 mL was layered over 10 mL of 1.2 M sucrose. These tubes were centrifuged in an L7-65 ultracentrifuge using a 50.2 Ti rotor at 4 °C for 29 min at 44 000 rpm. The layer at the interface was then removed and subjected to a second sucrose spin over 0.8 M sucrose. The pellet was resuspended in TME buffer (25 mM Tris base, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.4), aliquoted, and stored at -70 °C. Protein was determined using the method of Markwell et al.

2. [^{35}S]GTPγS Binding Assay. The rat membrane preparation (40-50 μg of protein) was incubated for 1 h at 30 °C in assay buffer (10 mM Tris, 100 mM NaCl, 5 mM $MgCl_2$, 0.1% BSA) with 50 μL of 50 μM GDP, 50 μL of 0.05 nM [^{35}S]GTPγS, or 100 μL of either; 10 μM GTPγS was used to measure the nonspecific binding, a series of different concentrations of the analogues being tested, or buffer alone as a control to obtain the baseline of GTPγS stimulation. The reaction was terminated by rapid filtration through Whatman GF/B filters, with ice-cold wash buffer containing 0.5% bovine serum albumin using the Packard Filtermate. Bound radioactivity was measured on the Packard Top-Count microplate scintillation counter.

TABLE 2 illustrates EC_{50} values of inventive compounds 1, 3 and 11 for stimulating [^{35}S] GTPγS binding in rat microsomal membranes. The results are shown graphically in Figure 5.

TABLE 2

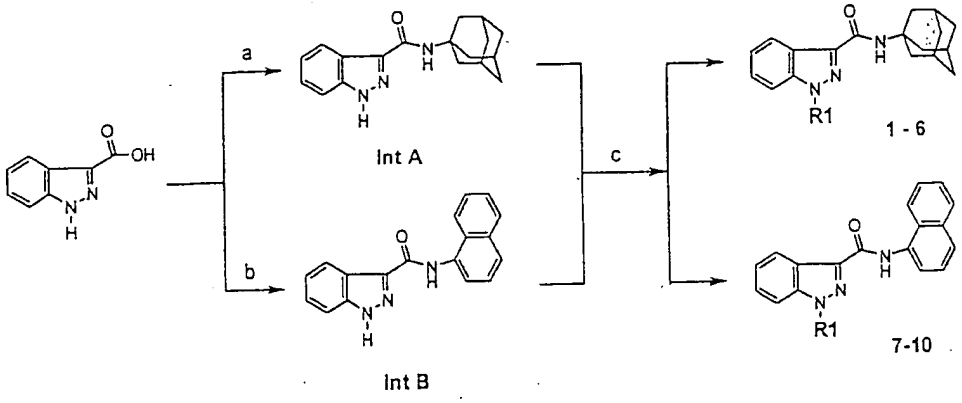
compound	EC50(μM)		
	Y	SD	N
1	13.088	8.959	3
3	15.600	7.142	3
11	17.973	4.655	3

Preparation of compounds

General. Column chromatography was carried out by using active silica gel (230–400 mesh) available from Selecto Scientific of Suwanee, Georgia. Eluents were distilled before use. Solvents for reactions were dried or purified as required. Reactions were carried out under argon atmosphere unless otherwise noted. All of the reagents are available from Sigma-Aldrich Fine Chemicals of Milwaukee, Wisconsin and/or Lancaster Synthesis Inc. of Windham, New Hampshire.

General procedure for the preparation of compounds 1-10:

Scheme 1:



(a) $CO(imd)_2$/DMF, adamantamine; (b) 1-HOBt, WSCD.HCl, DMF, 1-aminonaphthalene; (c) NaH/DMF, RX (alkyl halide)

Int A.

To a magnetically stirred solution of 1*H*-Indazole-3-carboxylic acid (1 g, 6.17 mmol) in DMF (15 mL) was added 1,1'-carbonyldiimidazole (1.1 g, 6.78 mmol) in one

portion. The resulting solution was warmed at 60 °C for 2 hours (h) and then cooled to room temperature before adding a suspension of adamantamine (0.932 g, 6.17 mmol) in DMF (20 mL). The resulting solution was heated at 60 °C for 2 h. The DMF was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2. The solution was washed sequentially with water, 1 N NaOH solution, water, and brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was recrystallized from EtOH to give the expected Int A.

Int B.

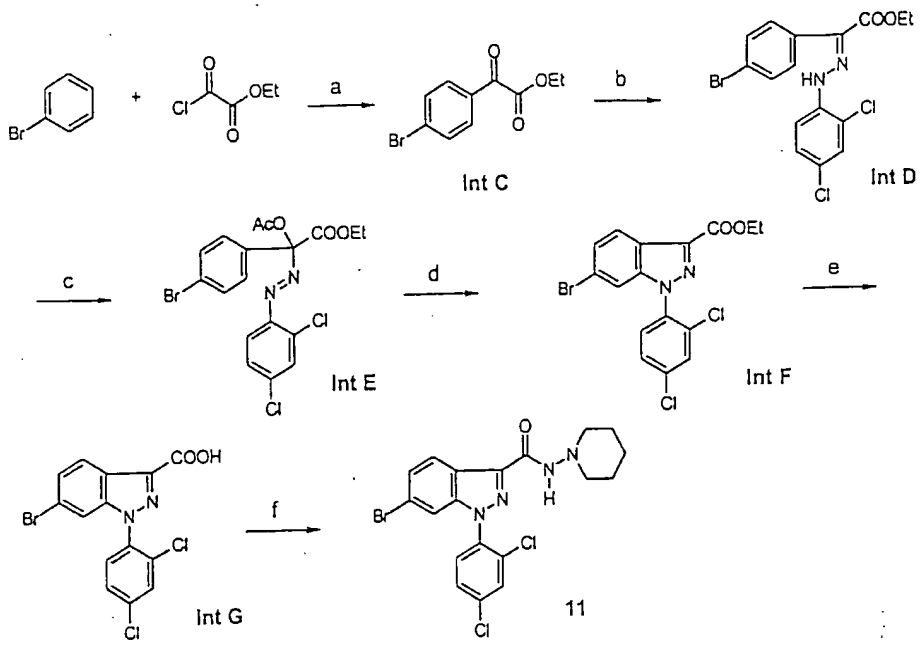
To a magnetically stirred solution of 1*H*-Indazole-3-carboxylic acid (3.00 g, 18.5 mmol), 1-aminonaphthalene (2.65 g, 18.5 mmol) and 1-hydroxybenzotriazole (HOBt; 3g, 22.2 mmol) in dry DMF (45 mL) was added 1-ethoxy-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSCD.HCl; 3.9 g, 20.3 mmol) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 2 h. After stirring for 2 h brine was added and the mixture was extracted multiple times with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash column chromatography on silica gel gave the expected Int B.

Final compound 1-10:

To a magnetically stirred solution of 0.51 mmol of Int A or B in 2 mL of DMF at room temperature was added NaH (60% dispersion in mineral oil, 25 mg, 0.63 mmol). The resulting mixture was allowed to stir at room temperature for 3 h. The reaction mixture was cooled to about 20 °C, and RX (0.56 mmol) was added. The resulting solution was allowed to stir at room temperature for about 18 h. The DMF was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2. The solution was washed sequentially with 10% aqueous sodium carbonate solution, water and brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give an oil. The resulting product was purified by flash column chromatography.

General procedure for the preparation of compound 11:

Scheme 2:



(a) $AlCl_3/CH_2Cl_2$; (b) HAc/MeOH, 2,4-dichlorophenylhydrazine; (c) $Pb(OAc)_4/CH_2Cl_2$; (d) $BF_3.Et_2O/Et_2O$; (e) KOH/H_2O, then HCl/H_2O; (f) $CO(imd)_2$/DMF, 1-aminopiperidine.

Int C.

Bromobenzene (2.1 g, 13 mmol), 2.6 g (19 mmol) of ethyl oxalyl chloride, and 25 mL of anhydrous methylene chloride were placed in a 50 mL flask equipped with a magnetic stirrer and suspended in an ice-salt bath. After the solution was stirred for 10 min, 3.4 g (25 mmol) of aluminum chloride was added in small portions over 10 min. When the solution turned red-brown and became homogenous, the ice-salt bath was removed and the mixture was poured over 100 g of crushed ice and 50 ml of concentrated hydrochloric acid. The decomposed mixture was washed with 30 mL of 0.1 N sodium hydroxide three times. After the organic layer was separated and the solvent was evaporated, the crude product was purified by column chromatography to give Int C.

Int D.

Ethyl phenylglyoxylate (1.1 g, 4.28 mmol) was added to a mixture of 2,4-

dichlorophenylhydrazine (0.78 g, 4.39 mmol) and 90% acetic acid (1 mL) and the solution refluxed for 30 min. Ethyl phenylglyoxylate 2,4-chlorophenylhydrazone (Int D) crystallized on cooling.

Int E.

A solution of Int D (1.27 g, 3.05 mmol) in dichloromethane (10 mL) was added to a stirred mixture of lead tetraacetate (3.59 g) and dichloromethane (20 mL), keeping the temperature between 0 °C and 10 °C. The mixture was heated for 15 min at 20-25 °C; water and dilute HCl were then added with the temperature kept below 25 °C. The organic layer was separated and the solvent evaporated. Purification by flash column chromatography on silica gel gave the expected Int E.

Int F.

Boron trifluoride etherate (10 mL) was added dropwise to a stirred solution of Int E (1.22 g, 2.57 mmol) in ether (25 mL), keeping the temperature at 0 °C. The mixture was refluxed for 20 min, poured into water, and stirred until complete evaporation of ether has occurred. Int F was separated and purified by flash column chromatography on silica gel.

Int G.

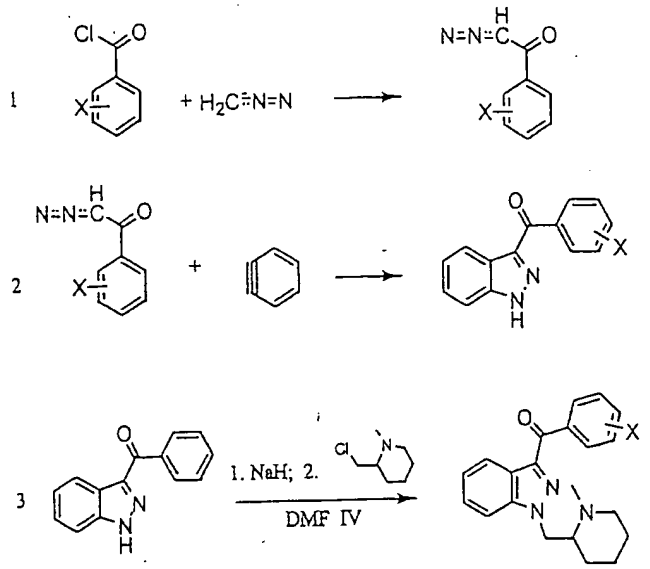
A mixture of the above ester (0.928 g, 2.24 mmol), 10% KOH aqueous (3 mL), and methanol (15 mL) was refluxed for 3 h. The cooled solution was acidified with 6 N HCl. The precipitate was collected and purified by flash column chromatography on silica gel to give Int G.

Final compound 11.

Compound 11 was prepared by following the procedure a of Scheme 1 by using 1-aminopiperidine instead of adamantamine.

Synthesis 3-aroyl substituted indazoles via cycloaddition of diazoketones with benzyne.

The methodology of this approach is showed below:



A suspension of phenyldiazonium carboxylate (5 mmol) and appropriate diazoketone (2.5 mmol) is stirred and heated at 40 °C in 20 ml methylene chloride for approximately 6 h **Caution! Phenyldiazonium carboxylate is highly explosive in a dry form. Do not dry phenyldiazonium carboxylate after it is synthesized !** To the reaction mixture 30 ml of water is added and products are extracted with ethyl acetate (3x10 ml). The combined organic extract is washed with water, washed with brine, dried with sodium sulphate and evaporated to dryness to give a dark oil or solid. The desired product is isolated and purified using preparative column chromatography on silica gel (petrol ether – ethyl acetate). Alkylation of the prepared product is the same as for the synthesis of indole derivatives.

Results of Antinociception Activity

Using rats as test subjects, varied doses of some of the inventive compounds were injected subcutaneously in the dorsal surface of the paw (i.paw, 50 µl). Measurements were taken 25 min after i.paw injection. Assessment of antinociceptive action was made by evaluating the response latency to removal of the paw from a focused source of thermal stimulation, as described by T. P. Malan Jr., CB2 Cannabinoid Receptor-mediated Peripheral Antinociception, Pain, 93, 239-245 (2001), the content of which is incorporated by reference herein. Rats were

allowed to acclimate within Plexiglas enclosures on a clear glass plate maintained at 30 °C. A radiant heat source (a high-intensity projector lamp) was focused onto the plantar surface of the hindpaw. Activation of the heat source activated a timer, which stopped when withdrawal of the paw was detected with a photodetector. A maximal cut-off of 40 seconds (s) was utilized to prevent tissue damage.

Antinociception is expressed as the percent of the maximum possible effect (%MPE), using the formula: %MPE=(WL-CL)/(CO-CL), where WL is the withdrawal latency obtained experimentally, CL is the control (baseline) value before drug administration, and CO is the cut-off value (40 s). Dose-response curves were generated. Significance was defined as $P<0.05$.

As shown in Figure 1, compound 3 produced dose-dependent antinociception to a thermal stimulus applied to the hindpaw, when administered into the hindpaw on the side of testing (ipsilateral i.paw). As shown in Figure 2, compound 2 produced the similar dose-dependent antinociception to a thermal stimulus but was less potent than compound 3.

This antinociception and analgesic effect is attributed to the interactions of the inventive compounds with the CB1 and/or CB2 receptors. The higher affinities for cannabinoid receptors observed in compound 3 as compared to compound 2 are reflected in the more potent ability of compound 3 to produce analgesic effects (see Figures 1 and 2) as compared to compound 2. It should be noted that CB2 selective compounds can produce pharmacological effects by preferential interaction with the CB2 receptors without producing CNS effects. Non-selective compounds will also produce pharmacological effects, although the effects will be associated with both CB1 and CB2 receptors.

Results of Locomotor Activity

Rats were injected with varied doses of either some of the inventive compounds or with WIN 55212-2, a known CB1/CB2 receptor agonist. The injected compounds were solubilized in DMSO:40% cyclodextrin (1:10) and intravenously administered.

Locomotor activity was assessed by measuring the rate of beam crossings by rats in a photocell apparatus according to the procedure of M. Cosenza et al, Locomotor Activity and Occupancy of Brain Cannabinoid CB1 Receptors by the

Antagonist/Inverse Agonist AM281, Synapse, 38, 477-482 (2000).

As shown in Figure 4, WIN 55212-2, a known CB1/CB2 receptor agonist, significantly reduced locomotor activity early after administration. As shown in Figure 3, inventive compound 3 similarly significantly reduced locomotor activity early after administration.

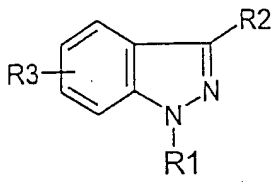
Both WIN 55212-2 and compound 3 acted as cannabinoid agonists in the locomotor assay and produced the typical cannabinoid-like catalepsy and inhibition of locomotion. For compound 3 this locomotor effect is attributed to the interaction of that compound with the CB1 receptor in the central nervous system.

The inventive heteroindane analogs described herein also have potential as immunomodulating drugs and antiinflammatory agents. Additionally, the inventive heteroindane analogs described herein can be used in the treatment of, for example, marijuana abuse, obesity, stress, vomiting, thymic disorders, dyskinesia, anxiety disorders, psychotic disorders, cognitive disorders, mood disorders, delirious disorders, psychosomatic-induced disease, epilepsy, glaucoma, nausea associated with cancer chemotherapy and AIDS wasting syndrome and other ailments in which cannabinoid system is implicated as well as for treatment of alcohol, opioid, nicotine and cocaine addiction, etc

While preferred embodiments of the foregoing invention have been set forth for purposes of illustration, the foregoing description should not be deemed a limitation of the invention herein. Accordingly, various modifications, adaptations and alternatives may occur to one skilled in the art without departing from the spirit and scope of the present invention.

What Is Claimed Is:

1. A compound of formula I below, and physiologically acceptable salts, comprising:



wherein,

R1 comprises –Q–Z;

Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present;

Z comprises, in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino;

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

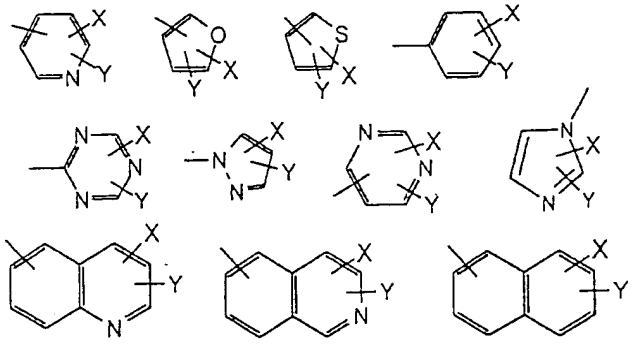
X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above

group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group comprising a substituent group on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2;

R2 comprises $-Q_1-het-Q_2-Z$;

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

het comprises O, N or S;

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

Z comprises, in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

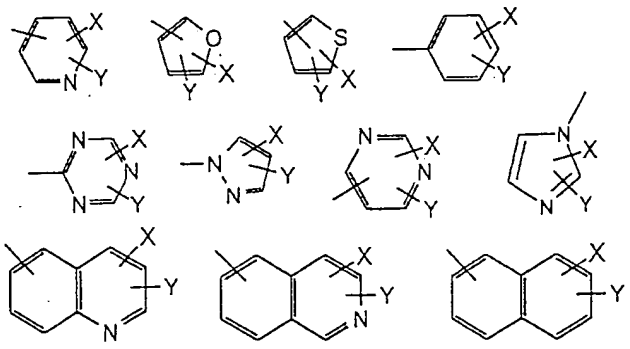
X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group,

a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; or

R2 comprises $-Q_1-X-Q_2-Z$;

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present and connected to a C, O or N atom in the X group;

X is optionally present and comprises any possible member selected from C(O), C(O)O, OC(O)O, NC(O)O, C(O)NT, NTC(O), OC(O)NT, C(O)NTT, C(O)NTNT, NTC(O)NT if present,

T comprises H, an alkyl group comprising 1 to about 4 C atoms, a heteroalkyl group comprising 1 to about 4 C atoms, a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members or a heteroaromatic ring having about 5 to about 7 ring members or any above group having a substituent group on at least one available ring atom;

Z comprises in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino,

X_1 and X_2 each independently comprise H or alkyl, or

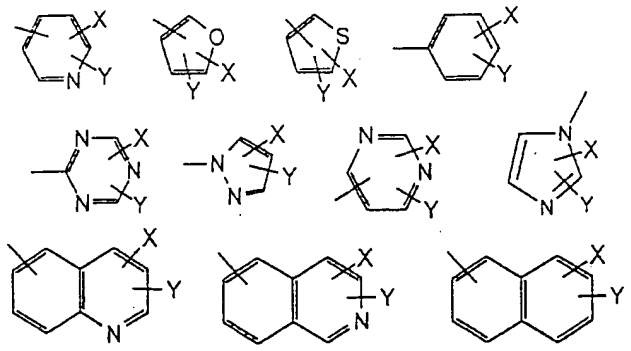
X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group comprising a substituent group on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; and

R3 comprises a substituent at any or all of the possible 4–, 5–, 6– and/or 7–positions, wherein each substituent is independently selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

2. The compound of claim 1 wherein R1 comprises -Q-Z; Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present; and Z comprises adamantyl or heteroadamantyl.

3. The compound of claim 1 wherein R2 comprises $-Q_1-het-Q_2-Z$; and Z comprises adamantyl or heteroadamantyl.

4. The compound of claim 1 wherein R2 comprises $-Q_1-X-Q_2-Z$ and Q_1 comprises an alkyl group having 1 to about 5 carbon atoms if X is CO.

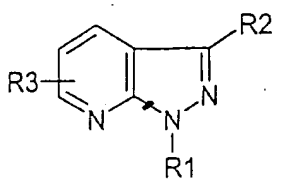
5. The compound of claim 1 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises adamantyl or heteroadamantyl.

6. The compound of claim 1 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl having independently selected substituent groups in at least one of the 2 and 5 positions.

7. The compound of claim 1 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl substituted with a heteroaromatic moiety.

8. The compound of claim 1 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl substituted in one of the 2 or 5 position with a heteroaromatic moiety and in the other of the 2 or 5 position with a halogen.

9. A compound of formula II below, and physiologically acceptable salts, comprising:



wherein,

R1 comprises –Q–Z;

Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present;

Z comprises, in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino;

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

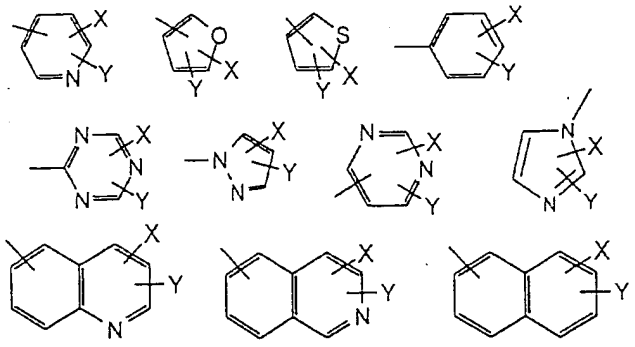
X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and

independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group comprising a substituent group on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2;

R2 comprises $-Q_1-het-Q_2-Z$;

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

het comprises O, N or S;

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

Z comprises, in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

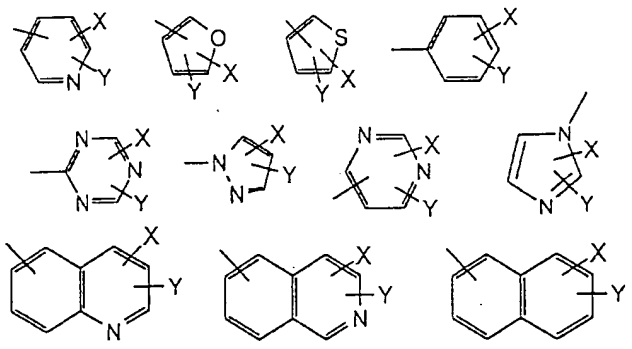
X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted

phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; or

R2 comprises $-Q_1-X-Q_2-Z$;

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present and connected to a C, O or N atom in the X group;

X is optionally present and comprises any possible member selected from C(O), C(O)O, OC(O)O, NC(O)O, C(O)NT, NTC(O), OC(O)NT, C(O)NTT, C(O)NTNT, NTC(O)NT if present,

T comprises H, an alkyl group comprising 1 to about 4 C atoms, a heteroalkyl group comprising 1 to about 4 C atoms, a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members or a heteroaromatic ring having about 5 to about 7 ring members or any above group having a substituent group on at least one available ring atom;

Z comprises in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino,

X_1 and X_2 each independently comprise H or alkyl, or

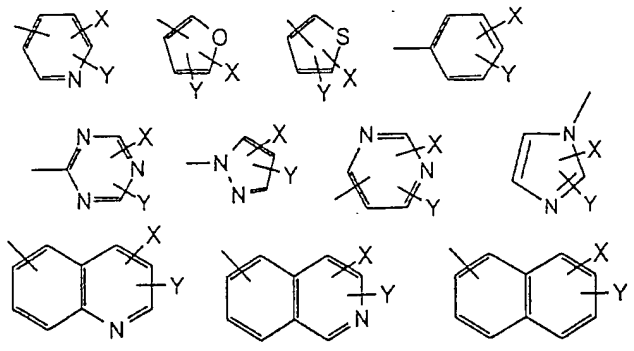
X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3,

$COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group comprising a substituent group on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; and

R3 comprises a substituent at any or all of the possible 4–, 5–, 6– and/or 7–positions, wherein each substituent is independently selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

10. The compound of claim 9 wherein R1 comprises -Q-Z; Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present; and Z comprises adamantyl or heteroadamantyl.

11. The compound of claim 9 wherein R2 comprises $-Q_1-het-Q_2-Z$; and Z comprises adamantyl or heteroadamantyl.

12. The compound of claim 9 wherein R2 comprises $-Q_1-X-Q_2-Z$ and Q_1 comprises an alkyl group having 1 to about 5 carbon atoms if X is CO.

13. The compound of claim 9 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises adamantyl or heteroadamantyl.

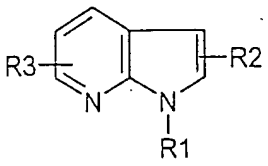
14. The compound of claim 9 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl having independently selected substituent groups in at least one of the 2 and 5 positions.

15. The compound of claim 9 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl substituted with a heteroaromatic moiety.

16. The compound of claim 9 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl substituted in one of the 2 or 5 position with a heteroaromatic moiety and in the other of the 2 or 5 position with a halogen.

17. The compound of claim 9 wherein R2 comprises $-Q_1-X-Q_2-Z$ and Q_1 comprises an alkyl group having 1 to about 5 carbon atoms if X is CO.

18. A compound of formula III below, and physiologically acceptable salts, comprising:



wherein,

R1 comprises $-Q-Z$;

Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present;

Z comprises, in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino;

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

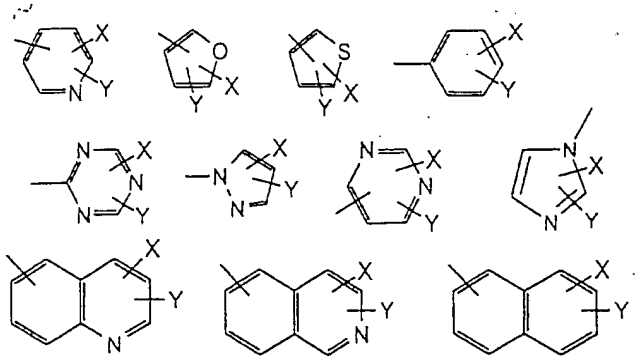
X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group,

a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group comprising a substituent group on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino

or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2;

R2 comprises $-Q_1-het-Q_2-Z$;

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

het comprises O, N or S;

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

Z comprises, in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

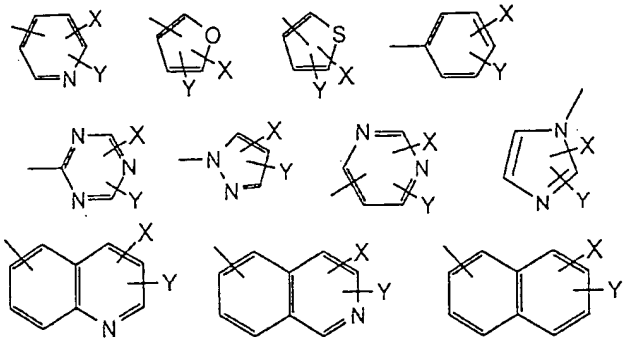
X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group;

or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; or

R2 comprises $-Q_1-X-Q_2-Z$;

Q_1 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present;

Q_2 comprises an optionally present alkyl group having 1 to about 5 carbon atoms if present and connected to a C, O or N atom in the X group;

X is optionally present and comprises any possible member selected from C(O), C(O)O, OC(O)O, NC(O)O, C(O)NT, NTC(O), OC(O)NT, C(O)NTT, C(O)NTNT, NTC(O)NT if present,

T comprises H, an alkyl group comprising 1 to about 4 C atoms, a heteroalkyl group comprising 1 to about 4 C atoms, a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members or a heteroaromatic ring having about 5 to about 7 ring members or any above group having a substituent group on at least one available ring atom;

Z comprises in any possible position, any possible member selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $C(O)OX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino,

X_1 and X_2 each independently comprise H or alkyl, or

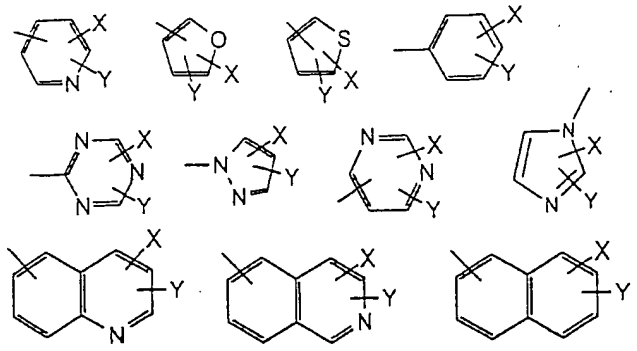
X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; or any above group substituted on at least one available ring carbon atom by an alkyl group and independently substituted on at least one available ring nitrogen atom by at least one of an alkyl group, a benzyl group, a lower-alkoxybenzyl group, a benzhydryl group, a substituted benzhydryl group, a phenyl group, a substituted phenyl group, a methylbenzyl group, a substituted methylbenzyl group; and wherein the connecting point to the Z group can be any possible ring atom; or

Z comprises, in any possible position, any possible member selected from



wherein X and Y in the Z structure each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2; or

Z comprises, in any possible position, any possible member selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group comprising a substituent group on at least one available ring atom; and wherein the connecting point to the Z group can be any possible ring atom; and

R3 comprises a substituent at any or all of the possible 4–, 5–, 6– and/or 7–positions, wherein each substituent is independently selected from H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, acyl, substituted acyl, aroyl, substituted aroyl, heteroaroyl, substituted heteroaroyl, O-acyl, O-aroyl, OalkylOH, $OalkylNX_1X_2$, NH-acyl, NH-aroyl, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

19. The compound of claim 18 wherein R1 comprises -Q-Z; Q comprises an optionally present alkyl group having 1 to about 7 carbon atoms if present; and Z comprises adamantyl or heteroadamantyl.

20. The compound of claim 18 wherein R2 comprises $-Q_1-het-Q_2-Z$; and Z comprises adamantyl or heteroadamantyl.

21. The compound of claim 18 wherein R2 comprises $-Q_1-X-Q_2-Z$ and Q_1 comprises an alkyl group having 1 to about 5 carbon atoms if X is CO.

22. The compound of claim 18 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises adamantyl or heteroadamantyl.

23. The compound of claim 18 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl having independently selected substituent groups in at least one of the 2 and 5 positions.

24. The compound of claim 18 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl substituted with a heteroaromatic moiety.

25. The compound of claim 18 wherein R2 comprises $-Q_1-X-Q_2-Z$; and Z comprises phenyl substituted in one of the 2 or 5 position with a heteroaromatic moiety and in the other of the 2 or 5 position with a halogen.

26. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound selected from claim 1, claim 9 or claim 18, or a physiologically acceptable salt thereof.

27. A method of stimulating a cannabinoid receptor in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of at least one compound selected from claim 1, claim 9 or claim 18, or a physiologically acceptable salt thereof.

28. A method of selectively stimulating CB2 cannabinoid receptors in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of at least one compound selected from claim 1, claim 9 or claim 18, or a physiologically acceptable salt thereof.

29. A method of treating a condition selected from central pain, peripheral pain, inflammatory pain, neuropathy, a neurodegenerative disease, a mental disorder, a disease associated with motor function, inflammation, epilepsy; glaucoma; nausea associated with cancer chemotherapy; nausea associated with AIDS wasting syndrome; or of reducing endotoxic shock; or of reducing hypotensive shock; or of modulating appetite; or of reducing fertility; or of providing neuroprotection; or of suppressing memory; or of producing peripheral vasodilation: comprising administering to an individual or animal having the conditon a therapeutically effective amount of at least one compound selected from claim 1, claim 9, claim 18, or a physiologically acceptable salt thereof.

30. Use of a therapeutically effective amount of at least one compound selected from claim 1, claim 9, claim 18, or a physiologically acceptable salt thereof as an immunomodulating drug or an antiinflammatory agent.

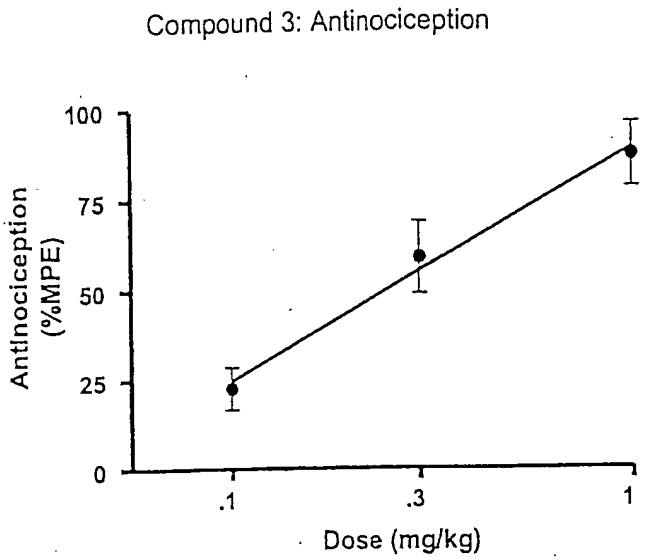


Figure 1: Peripheral antinociceptive effect of compound 3. Compound 3 was injected into the hindpaw ipsilateral to the side of nociceptive testing. Data expressed as mean ±SEM. *N* = 6 per group.

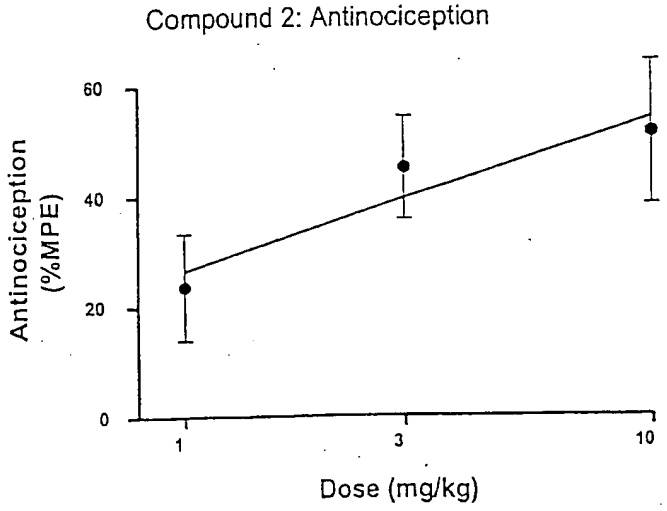


Figure 2: Peripheral antinociceptive effect of compound 2. Compound 2 was injected into the hindpaw ipsilateral to the side of nociceptive testing. Data expressed as mean ±SEM. *N* = 6 per group.

Compound 3: Locomotor Activity

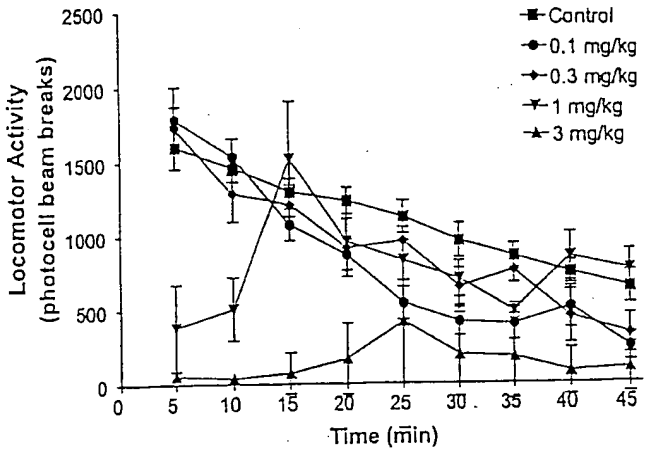


Figure 3: Compound 3 effects on time-course of locomotor activity. The line graph shows locomotor activity in five groups of mice that were treated with control only, and different doses of drugs (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg and 3 mg/kg). Y-axis values are mean ±SD beam crossings per minute in 5-min periods for at least nine pairs of animals per group.

WIN 55212-2: Locomotor Activity

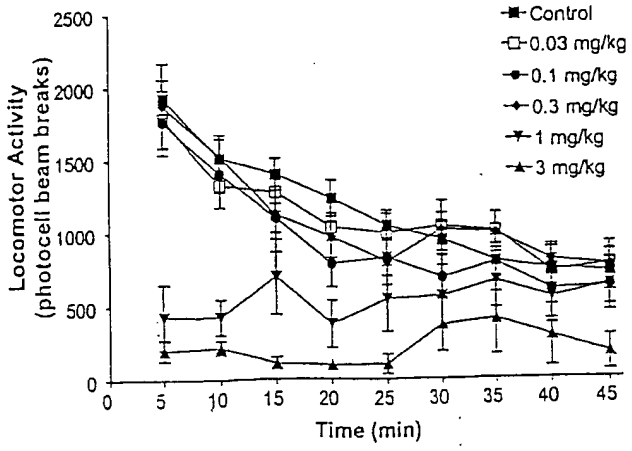


Figure 4: WIN 55212-2 effects on time-course of locomotor activity.

Figure 5.